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Multiple Central Nervous System Haemangioblastomas

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Luana Padovan, MD (Paediatric Resident)

Deborah G., a 13-year-old white female, was referred to a local hospital at the beginning of April 1994, because of a 3-month history of morning headache and vomiting. Three weeks before admission, she also started to complain of dizziness and increasing gait instability. A computed tomography (CT) scan of the brain was obtained, and a posterior fossa cystic mass, associated with triventricular hydrocephalus, was documented, and she was referred to this unit.

On admission, her physical and neurological examinations were positive only for mild truncal and extremity ataxia and dysmetria associated with gait instability. Bilateral florid papilloedema with bilateral retinal haemorrhages were also documented. Her previous medical and family histories were unremarkable, but the maternal grandfather suffered what was referred to as a cerebellar haemorrhage at the age of 70 years. Unfortunately, her grandfather's old medical record yielded no further information as to the cause of that haemorrhagic event. The patient's symptoms rapidly recovered after steroid therapy, and the day after admission a magnetic resonance image (MRI) of the brain was obtained. Dr. Carollo, could you please comment on those initial neuroradiological findings?

Carla Carollo, MD (Paediatric Neuroradiologist)

The head CT scan done in the local hospital shows a large hypodense mass in the posterior fossa, measuring 3 × 3 cm. There is a surrounding hypodense ring and moderate perilesional edema (Fig. 1). This mass causes triventricular hydrocephalus. The MRI shows that the tumour involves the inferior aspects of the vermis and the cerebellar peduncles, compresses the fourth ventricle, and reaches the foramen magnum (Fig. 2). The lesion has a prevalent septated cystic component and a solid mural nodule. Both the nodule and the thick cyst wall enhance briskly after gadolinium infusion. There are also some scattered foci of signal voiding representing anomalous vessels, the largest being located on the posterior surface of the lesion. Three small bright nodules in the occipital cortex and on the spine at the level C1-C2 and C3-C4 are also visible. Furthermore, a syrinx was noted for almost the entire length of the visualized spine (Fig. 3). Because of this finding, we completed the study looking at the whole spine. The cord appears enlarged with a syrinx extending from the cervical down to the lumbar region. After gadolinium, many enhancing nodules are seen at the cervical and thoracic levels, the largest one (diam. 11 × 17 mm.) being located at the level of T5-T6, inside the syrinx (Fig. 3).

Giorgio Perilongo, MD (Paediatric Neuro-Oncologist)

Did the child have any symptoms or signs that could have led us to suspect the presence of such a large spinal lesion at the T5-6 level?

Antonio Battistella, MD (Paediatric Neurologist)

The only signs possibly indicative of those lesions were the decrease of tactile and pain sensation at the level of T6-T9 and the absence of the superficial reflexes bilat-

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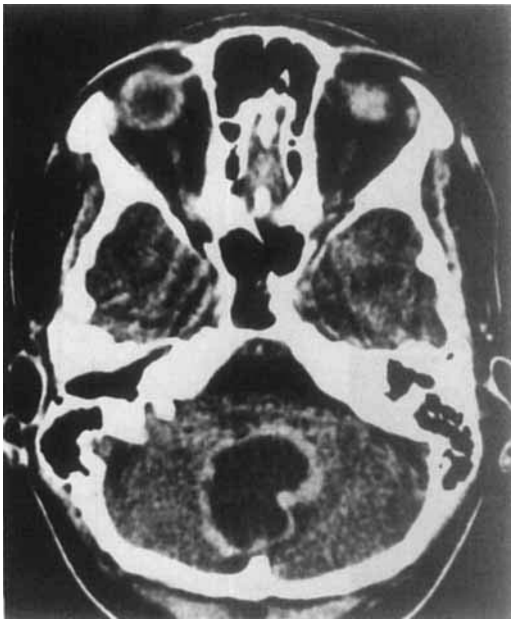

Fig. 1. Cerebral computed tomography scan after contrast material injection. Large cerebellar hypodense (cystic) mass with enhancing ring and mural nodules.

erally. No other sensory and motor abnormalities or sphincteral dysfunction were present.

Dr. Perilongo. What is the differential diagnosis of a cystic lesion of the posterior fossa? Could these nodules we see along the spine be interpreted as signs of leptomeningeal tumour dissemination?

Dr. Carollo. In the pediatric age group, astrocytoma, haemangioblastoma (HGB), and ependymoma should be considered in the differential diagnosis of a ringlike enhancing tumour of the posterior fossa. Other rare conditions that could be considered are choroid plexus papilloma, atypical (cystic) medulloblastoma, abscess, malignant lymphoma, and giant aneurysm. The cyst wall of a HGB rarely shows uptake of contrast material unlike what happens with a cerebellar astrocytoma. Thus if one looks only at the posterior fossa images, it would be tempting to make the diagnosis of a classic cystic cerebellar astrocytoma. However, multiple leptomeningeal and spinal nodules along the syringococele, i.e., the central canal of the spinal cord, may be read as metastatic nodules of a malignant posterior fossa cystic tumour. With this hypothesis in mind, malignant astrocytoma, ependymoma, or atypical cystic medulloblastoma should be considered high on the list of tumours capable of such diffuse tumour seeding. It is, however, very rare to have these tumours metastasizing so diffusely at presentation. I, therefore, think the most likely diagnosis is a condition marked by multifocal lesions, which in this case leads me to multiple HGBs. Those lesions can grow in the leptomeningeal space as well as within the syringococele.

Dr. Battistella. Was the red blood cell count within normal limits? I ask this because it is reported that about 10% of central nervous system (CNS) HGB are associated with polycythemia, secondary to erythropoietin tumour production [1].

Dr. Padovan. Her red blood cell counts and haemoglobin value were within normal limits (RBC 4,028,000 ml and Hb 12.3 g/100 ml). The child was then admitted to surgery. Can you describe what you found macroscopically, Dr. Pellone, and can you then report the pathology findings, Dr. Gardiman?

Mario Pellone, MD (Paediatric Neurosurgeon)

The tumour was reached through a suboccipital approach. The cerebellum was compressed. After superior dislocation of the vermis, a bloody, dark red tumour covered by vessels appeared. Initially, the cysts, containing a xanthochromic liquid, were drained. Then, after clamping the main vessels supplying the mass, the tumour was macroscopically removed without any major bleeding.

Marina Gardiman, MD (Neuropathologist)

Microscopically, the neoplasm is composed of thin, dilated capillaries and thick cavernous-type vessels lined by hyperplastic endothelial cells and pericytes. Those vessels surround nests or lobules or large stromal cells (Fig. 4). These cells have a cytoplasm rich in lipid with pleomorphic nuclei (Fig. 5). These are no mitoses, areas of necrosis or gliosis, and no Rosenthal fibres. A honeycomb-like reticular pattern was visible with thin collagenous septae often surrounding individual cells. The cystic wall was composed of fibrous tissue and reactive astrocytes. Those findings are in favour of a cystic HGB. The immunohistochemistry analysis of the stromal cells revealed scanty glial fibrillary acid protein (GFAP) positivity. It remains a matter of discussion whether this reactivity reflects glial differentiation or GFAP uptake by phagocytes, as some authors have suggested [2]. No epithelial membrane antigen (EMA) positive cells, typical of metastatic renal cell carcinoma, were seen. Finally, no evidence of invasion of normal cerebellar parenchyma was noted.

HGB, or actually capillary HGB, is a rare, benign tumour of the CNS, which always recalls the von Hippel Lindau syndrome (VHL). According to various series, it accounts for 1.1–2.4% of all CNS neoplasms [2]. Cerebellar HGB represents 1–2% of all posterior fossa tumours; however, in adults its incidence rises to 7%, thus being as common as meningioma. In patients affected by VHL, the incidence of HGB has been reported as high as >60% [3]. The proportion of patients with CNS HGB affected by VHL varies from 21% to 72% according to different authors [3]. HGB can be diagnosed at any age, but usually the disease affects adults in their fourth de-

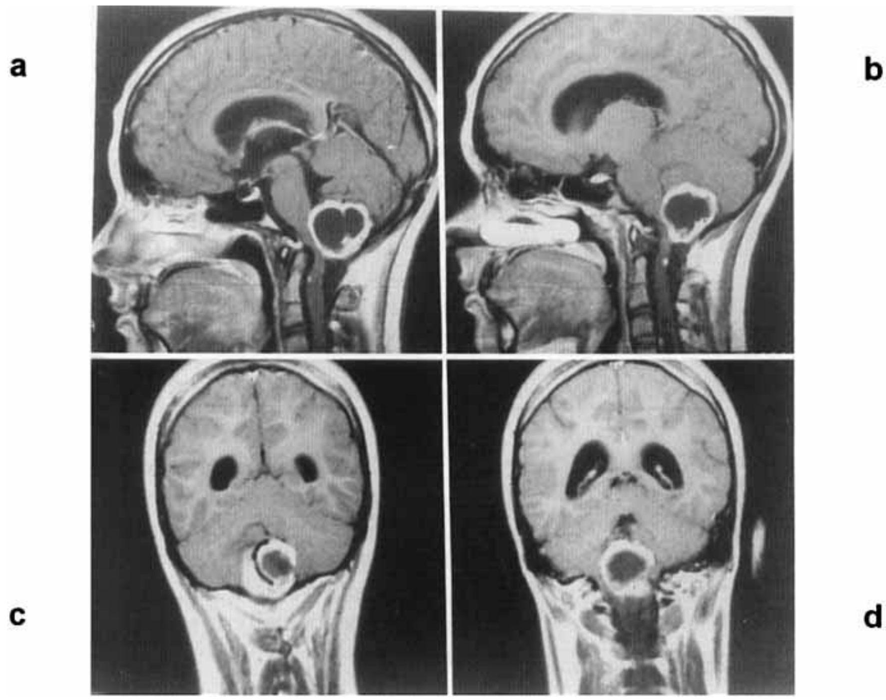

Fig. 2. Cerebral MRI: sagittal (**a,b**) and coronal (**c,d**) gadolinium-enhanced T_1 weighted images. A midline large cystic lesion with an enhancing thick wall and septation is visible in the posterior fossa, involving the inferior part of the vermis, compressing the medulla and reaching the foramen magnum. Small enhancing nodules are seen in the occipital cortex and on the cervical cord anteriorly and posteriorly.

cade of life without any clear sex prevalence [2,3]. Patients with multiple HGB tend to be younger than the ones with a single focus, and they are also more likely to have VHL.

The vast majority of HGB occur in the posterior fossa and can originate anywhere in the cerebellum. However, they have been described practically everywhere within the CNS, including the brainstem, the spine, and rarely the supratentorial compartment, including the pituitary gland [4] and the optic nerves [5]. Cases of massive involvement of the CNS by HGB have been reported [3]. When located above the tentorium, the hemangioblastic variant of angioblastic meningioma should be considered in the differential diagnosis. Macroscopically, these tumours may present as a solid nodule, despite the fact that they are usually cystic. In the series of 93 HGB reported by Neumann [3], 75% were cystic and 25% solid; in the posterior fossa 86% were cystic as were 46% in the spine. All supratentorial HGB were solid.

It is worthwhile mentioning, because it occurred also in this girl, that the vast majority of spinal HGB are associated with syringomyelia [2,3]. Some have argued that syringomyelia is secondary to the same process that leads to tumour cyst formation and that the syrinx is part of VHL. However, a syrinx has never been described in patients with VHL without a spinal tumour also having been present [2,3].

Dr. Padovan. The postsurgical period was uneventful. After surgery her neurological examination was normal except for decreased tactile and pain sensation in the trunk and the absence of superficial reflexes. As mentioned, the histologic findings prompted us to consider the possible diagnosis of VHL. Abdominal ultrasound and detailed ophthalmologic examinations were therefore obtained. The abdominal ultrasound was normal, whereas at the ophthalmologic examination, retinal haemorrhages (as already mentioned) were documented.

Luisa Pinello, MD (Paediatric Ophthalmologist)

When I first examined the patient on the day of admission, I saw multiple, bilateral retinal haemorrhages and marked papilloedema. However, no HGBs were noted. A follow-up examination 1 month after the operation showed that the papilloedema and the haemorrhages had completely resolved, but once again, no HGBs were observed.

Retinal HGB in patients with VHL are usually multiple and are bilateral in more than half the cases. Because of their peripheral location, they are not always visible on direct fundoscopy, and often fluorescence angiography is needed. These retinal lesions can progressively compromise vision, provoking retinal detachment, vitreous haemorrhage, and macular edema and distortion. Because of all of this, retinal HGBs should be treated.

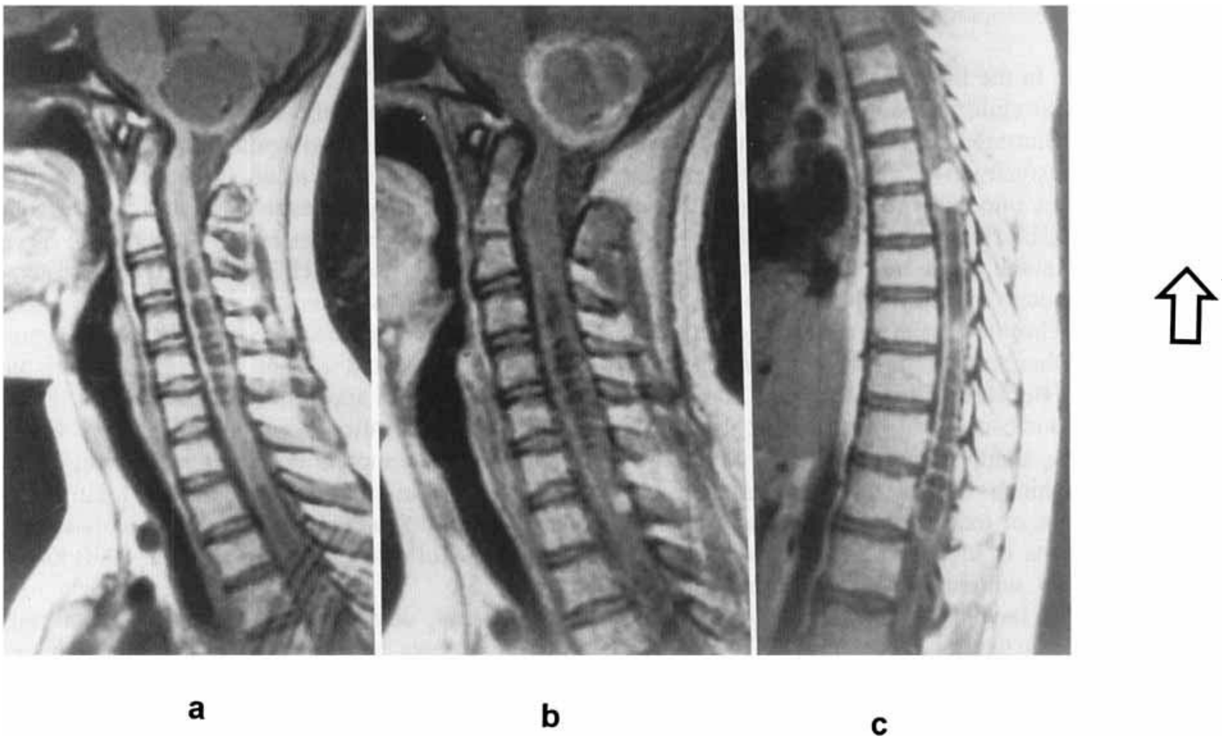

Fig. 3. Cervical and thoracic spine MRi-T1 weighted images before (**a**) and after (**b,c**) gadolinium enhancement. A large multiseptated syrinx involving the whole spine is visible. Many enhancing nodules are visible along the subarachnoidal space as well as within the syrinx, the largest one being located at the level of T_5-T_6 (c).

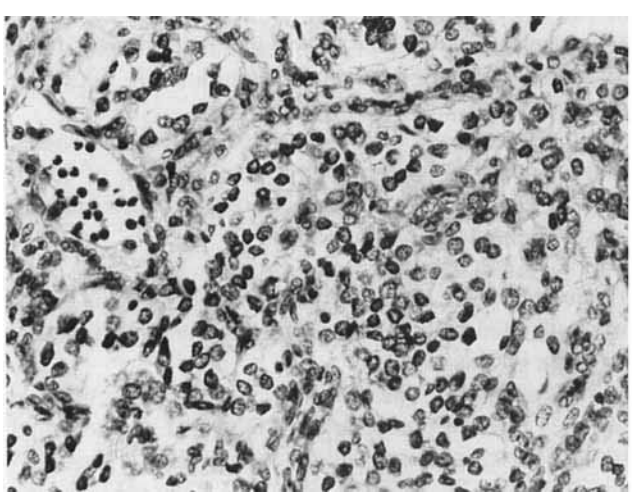

Fig. 4. Hemangioblastoma. A solid region of hemangioblastoma with a rich capillary network surrounding interstitial and stroma cells. (300×)

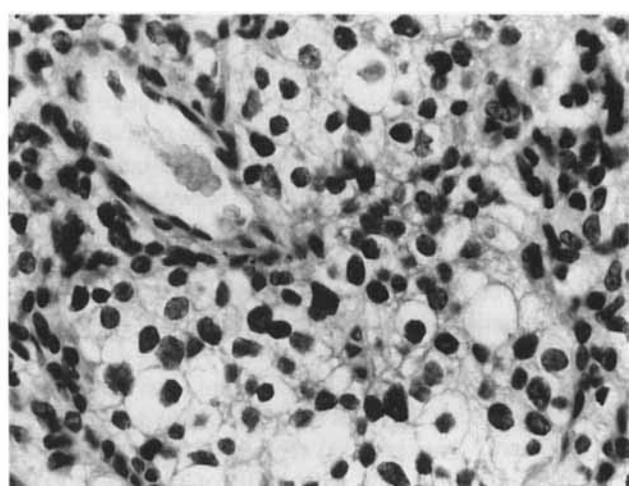

Fig. 5. Hemangioblastoma. Vacuolated lipid-rich stromal cells exhibiting pleomorphism and hyperchromatic nuclei. No mitoses are seen. (480×).

It is not uncommon for an ophthalmologist to be the first doctor to suspect VHL. In fact, quite frequently, patients affected by VHL initially seek medical attention because of the symptoms and signs related to retinal HGB. As is the case for cerebellar HGB, the earlier the diagnosis of retinal HGB is made, i.e., before the third decade of life, the more likely is VHL to be detected.

Screening of asymptomatic relatives of this girl is mandatory. Moore et al. [7] identified asymptomatic retinal HGB in 60% of affected patients with no previous

ophthalmologic investigations and in 30% of asymptomatic relatives.

Dr. Perilongo. In the light of these clinical findings, can we consider this child to be affected by VHL?

Dr. Padovan. Since the original description by Lindau in 1926 [8], the designation of VHL is restricted to those conditions in which one or more HGBs of the CNS are associated with HGB affecting one or both retinas. Additional findings in some cases are congenital cysts originating in the pancreas, kidneys, lung, liver, and epididymis and pheochromocytoma or renal cell carcinoma. However, since then, many phenotypic variants have been reported [9]. Because of this, in the past Russell and Rubinstein [2] hypothesized that "VHL in its classic form represents but one manifestation of a larger diversified nosologic entity which is essentially characterized by the development of one or more HGB: hence the term Haemangioblastomatosis is suggested for the overall condition." Cases of VHL without retinal involvement or extra CNS manifestations have been reported [3]. At least one family with a positive history of cerebellar HGB has been described, highlighting the occurrence of incomplete forms of the syndrome [2].

The criteria used to make the diagnosis of VHL disease in sporadic cases are: (1) single or multiple HGB of the retina and/or of the CNS, or (2) a single CNS or retinal HGB associated with a visceral lesion. However, in case of a positive family history of retinal or CNS HGB, the diagnosis of VHL is made if the patient is affected by a single HGB or a visceral lesion [1].

VHL is an autosomal dominant syndrome with a low new mutation rate. Its prevalence in the general population seems to be in the 1/36,000–1/50,000 range [10,11]. For every affected person, there are four or five relatives with a >25% chance of carrying the gene. Usually, patients are diagnosed with the syndrome between the second and fourth decade of life. Van der Hoeve included VHL among phacomatoses in 1933, and since then it has been always included in this group of diseases [12]. However, no specific cutaneous lesions have been reported in these patients.

The clinical stigmata of VHL are not always present at the time patients with HGB of the CNS are initially seen. Neuman and co-workers [3] reported that in almost half of the patients they saw with HGB of the CNS, extra-CNS lesions became evident only during the follow-up program. Of these patients, 21% at the time of the first neurosurgical intervention had no other manifestations of the syndrome. This is because the penetrance of the VHL is an age-dependent phemonenon, with 97% penetrance by 60 years of age [11].

Going back to the original question, in this girl the presence of multiple HGBs of the CNS and her young age, despite the lack of a clear family history and of retinal angiomatous lesions, strongly suggest the diagnosis of VHL. Obviously, only a molecular genetic analysis will confirm this hypothesis.

Dr. Battistella. What is the prognosis for this young girl? And in the light of the data emerging in the literature, how should the large spinal lesion be approached?

Dr. Padovan. There is no short answer to the first question. HGBs by themselves have a very favourable prognosis. They are benign lesions, and radical surgery is the cure. In fact, usually HGBs are well demarcated from the adjacent normal cerebral or cerebellar parenchyma, although foci of microscopic invasion may be present. Those findings could explain the rare cases of tumour recurrence after an apparent radical resection. HGB can definitively recur after incomplete resection. However, relapse after incomplete tumour resection may take decades to become clinically evident. At least two anecdotal cases of diffuse subarachnoid tumour dissemination after successful resection of a cerebellar HGB have been reported [2].

In the past, cerebellar HGB was the major cause of death in patients with VHL. It is thought that modern neuroimaging and neurosurgical techniques have dramatically improved matters. The morbidity and the mortality of HGB in patients affected by VHL can be related to their multiplicity and to the possible need of multiple neurosurgical interventions. As was said before, the earlier the diagnosis of VHL, the more likely is the possibility that new HGB will arise from time to time. The consequence is a higher likelihood that multiple surgical interventions will be needed. Stereotactic radiosurgical techniques are now emerging as valid alternatives to the classical neuro-surgical approach, particularly in cases of multiple, small, or relapsing HGB [13].

We have already said that retinal HGB may progressively jeopardize vision, being also a cause of severe morbidity. A variety of ophthalmologic approaches are now available to treat those lesions [5,6].

Finally, the overall prognosis of this girl, most likely affected by VHL, must also take into account the cancer risk associated with this syndrome. I ask Dr. Perilongo to comment on this problem.

Dr. Perilongo. The summary statement is this: we can't say anything more precise than that she is at high risk of developing renal cell carcinoma and/or pheochromocytoma just because she has VHL. Consequently, her ultimate prognosis will depend upon early diagnosis of those conditions (in case she develops them) and on the effectiveness of the monitoring program designed for her. The issues involved are far more complex, however, and I would like to share with you some of what I found in looking through the literature of this rare disease of childhood. We don't often have an opportunity to discuss HGB and VHL.

VHL is considered a family cancer syndrome with variable expression. Other than CNS and retinal HGB,

pheochromocytoma and renal cell carcinoma are the tumours occurring in VHL patients more frequently than in the normal population. VHL should be considered a growth disorder affecting specific organs and tissues and predisposing target organs to malignant transformation.

According to the age-dependent penetrance of the disease, it has been estimated that the cumulative risks of the population affected by VHL of developing retinal angiomas, cerebellar HGB, and renal cell carcinoma are 44%, 38%, and 5%, respectively, at 30 years of age, and 84%, 70%, and 69%, respectively, at 60 years [11]. Renal cell carcinoma is presently considered the main cause of death in VHL patients. The average frequency of pheochromocytoma is ~14%, ranging from 0 to >90% according to different series [14–17]. This means that the interfamilial differences in the occurrence of this tumour are particularly striking. Neumann et al. [17] recently published the results of a screening study. They used clinical criteria that included brain CT/MRI, abdominal US, direct ophthalmoscopy, and extensive pedigree analysis in looking for stigmata of VHL in an unselected series of patients affected by pheochromocytoma followed over a 22.5-year period [17]. Almost 20% of the study population proved to be VHL carriers. Half of them (53%) with VHL and pheochromocytoma had the tumour as the only manifestation of the disease. In the remainder, retinal HGBs were the most frequent findings, and in all cases they were asymptomatic.

As usually reported for those cancers associated with cancer family syndromes, such as retinoblastoma or this condition, they tend to occur at an earlier age than in the normal population. This is explained by the "two hit hypothesis" of Knudson [18], which postulates that the first of the two "hits" predisposing to cancer is present in the germ line. Furthermore, they tend to be multifocal and/or bilateral if paired organs (retina, kidney) are affected. Interestingly in the series from Neumann and colleagues [17], only a few of the pheochromocytomas affecting patients with VHL were malignant. None of them developed metastases, in comparison with 7 of the 63 patients with sporadic tumours [17].

The VHL gene has been identified at the 3p25-26 locus [19]. Genetically, this gene acts as a tumour suppressor gene. The exact biochemical function and its role in tumour development are not understood. The evidence seems to indicate that the VHL gene may be involved in signal transduction related to cell adhesion. The genomic sequence of the VHL gene is highly conserved throughout various species, from mammals to drosophila to the sea urchin [19–20]. This suggests that the VHL gene encodes a fundamental cellular function. Two transcripts of 6 and 6.5 Kb, respectively, have been identified. The 6 Kb transcript has been isolated in fetal brain, and the other in fetal kidney; both are expressed in adult tissue.

It is hypothesized that the diverse tumours associated with VHL share a common mechanism. Chromosome 3p allelic loss has been documented in HGB, renal cell carcinoma, pheochromocytoma, pancreatic tumours, and choroid plexus papillomas affecting patients with VHL [21,22]. The role of this genomic loss in sporadic tumours is unknown. Chromosome 3p allelic loss does not seem to occur in sporadic HGB. Mutation of the VHL gene has been documented in nonfamilial renal cell cancers [23]. However, molecular genetic evidence supports the hypothesis that at least three genetic loci on chromosome 3 contribute to renal cell carcinoma [23].

There is no evidence of locus etherogenicity. In fact, e.g., VHL families, regardless of their different predisposition to pheochromocytoma and renal cell carcinoma, all are linked to the 3p25-26 locus [24,25]. Thus it appears that the different phenotypes reflect allelic rather than locus etherogenicity.

Grossey et al. [26] recently correlated a specific genotype to the pheochromocytoma-prone phenotype. They documented that the substitution of an arginine at codon 238 by a tryptophane conveys a 62% risk of phenochromocytoma. Differently, large germline deletions, nonsense or frameshift mutations did not bring any excess of pheochromocytoma risk. Similar relationships between specific genotype and renal cell cancer phenotype have not been identified yet. Obviously, the documentation of specific relationships between genotype and phenotype will dramatically improve our capability of assessing individual cancer risks and targeting specific cancer prevention programs. In this context it is worthwhile mentioning that any statements regarding the existence of mutually exclusive clusters of anomalies and tumours in VHL patients have been systematically contradicted. Thus at the present time, no consistent predictions regarding the cancer risk of a single patient affected by VHL can be formulated based on patients' clinical characteristics at presentation.

I would also say that to explain the variety of anomalies and tumours found in VHL patients, some authors have advanced the hypothesis that this syndrome may be a "contiguous gene syndrome" whose prototype is the "WAGR" syndrome (Wilms' tumour, aniridia, genitourinary malformations, and mental retardation) [27]. Only further genetic analyses will be able to validate this hypothesis.

Other tumours that have been described in patients with VHL include CNS neuroepithelial tumours, ependymoma, astrocytoma and choroid plexus papilloma. However, except probably for choroid plexus papilloma, all the others seem to be coincidental findings [2,28,29].

Returning to the oncogenic potential of this syndrome, there are some clinical facts that should be stressed. First, at least three distinct clinical conditions expose the affected patients to a higher risk than the normal population of developing concurrent brain and renal tumours: tuber-

ous sclerosis, VHL, and the "rhabdoid tumour complex" [30]. Second, pheochromocytoma is a tumour "shared" by many cancer family syndromes: VHL, type I neurofibromatosis, tuberous sclerosis, Sturge-Weber disease, and multiple endocrine neoplasia type 2 (MEN 2). Except for MEN 2, all the other conditions are associated with some sort of growth and developmental disorders of the CNS [30]. It can be expected that a better understanding of the molecular genetic characteristics of these conditions will bring some order to what now seem to be unrelated bizarre biological and clinical phenomena.

Regarding your second question on the therapeutic approach to the spinal lesion, in principle I believe that a conservative surgical approach should be adopted for young patients affected by VHL, considering their potential need for multiple interventions. Another reason for caution is that the remaining growth potential of those lesions accidentally discovered is really unknown. However, in this case considering the large dimension of the spinal lesion and its critical location, I would consider it wise to remove it electively. Spinal HGBs can bleed, albeit the exact frequency of this complication is not known. Half the cases of spinal HGB reported by Neumann et al. [31] presented with subarachnoid bleeding. Most of these patients had minor neurological deficits. In a recent review of the literature on this problem, Yu et al. [32] collected seven cases of spinal bleeding by HGB (including the ones reported by Neumann) and added two personal observations of intramedullary haemorrhage. In the observed cases, bleeding was complicated by catastrophic neurologic effects despite prompt surgical intervention. The risk of spinal haemorrhage by itself is not commonly considered a criterion to remove all spinal HGBs at diagnosis. It should just be kept clearly in mind in the follow-up of these patients. Obviously, the ones that bleed should be removed. As Yu pointed out ". . . HGB must be considered among the differential diagnosis for a patient presenting with an intramedullary haemorrhage" [32].

The several complex issues associated with von Hippel-Lindau disease have been summarized recently by Maher [33].

Dr. Padovan. All the considerations just made highlight the problem of the optimal follow-up of these patients. We report a recently proposed protocol for monitoring VHL patients [3,6]: annual physical examination and urine testing; annual direct and indirect ophthalmoscopy with fluorescent angioscopy or angiography; MRI (or CT scan) of the brain every 3 years to age 50 and every 5 years thereafter; annual renal ultrasound, with CT scan every 3 years (more frequently if multiple renal cysts are present); and annual 24 hours urine collection for vanillylmandelic acid (VMA) levels.

For unaffected first-degree relatives, the following is proposed: annual physical examination and urine testing; annual direct and indirect ophthalmoscopy from the age of 5 years; annual fluorescent angioscopy or angiography from the age of 10 until age 60; MRI (or CT scan) of the brain every 3 years from ages 15–40 and then every 5 years until the age of 60; annual renal ultrasound with abdominal CT scan every 3 years from ages 20–65 years; and annual 24 hours urine collection for VMA.

There may be difficulties in achieving long-term compliance with this complicated long-lasting monitoring program, but follow-up and genetic counseling for these patients are needless to say, extremely important. We should accordingly recommend this surveillance program to our young female patient and her family.

It can be predicted with confidence that the expanding knowledge of the molecular genetic characteristics of the VHL will soon improve the precision of presymptomatic diagnosis of renal cell carcinoma and pheochromocytoma. Follow-up can then be made more specific for the early detection of the one or the other.

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Series Editor's Note

This Proceedings article is from the University of Padua, one of the oldest universities in Europe and known affectionately by the nickname "Il Bo".[1] It was officially established on September 29, 1222, although there seem to have been antecedent units for decades. Its formal establishment was occasioned by the exodus of several professors and students from the University of Bologna, which is the oldest university in continuous operation in the West and Near East, having been founded in 1088. The University of Alexandria in Egypt began much earlier, about 300 BC, centered around its incomparable library, but scholastic activities were interrupted when the library was destroyed in the third-century A.D.

The University of Padua, or Studium as it was called, became organized as a self-governing community of scholars with its own rules and regulations. The independence of the Studium was respected by the local civil authorities, and its strength in the community made it possible to withstand several attempts by various local and remote rulers to disband it over the centuries.

Students were organized into Nations. Those from the Italian peninsula were termed *Cismontanes*, and those from abroad were called *Ultramontanes*. The early history of the University shows it to be very heavily involved with studies of the law; in effect, therefore, both professors and students had strong voices in university affairs, since university rectors were drawn from the faculty of law. It took more than a century before studies of medicine, philosophy, and the humanities were recognized. The result was a division of the university into two units, each with its own rector. They were very powerful overseers of the academic activities and discipline of the university and had many specific duties in relation to the

[1]Bo = ox, because one of its early buildings of the university was a converted inn of that name.

conferring of degrees, teaching, and similar administrative functions.

The university had become a magnet for students from abroad, many of whom returned to their homelands to become famous theologians, jurists, physicians, and humanists. The same held true for the Italians, some of whom also became popes or cardinals. Testimony to its unswerving academic mission is the fact that the University of Padua was the first to grant a university degree to a woman. The doctorate in philosophy was granted to Elena Lucrezia Cornaro Piscopia in 1678.

The several faculties flourished, and the standing of medicine was advanced greatly at the beginning of the fourteenth century by Pietro d'Abano, who exercised a strong influence on the teaching of medicine, and therefore on medicine itself because of the hundreds of physicians who trained in Padua. A brief listing of the names of some of the teachers in the school of medicine and of the students—Vesalius, Fabricius, Falloppius, Morgagni, Copernicus, and William Harvey—gives some idea of the enormous impact the university had on science and on the theory and practice of medicine of that era. The influence of Padua on British medicine can be realized when it is noted that 80 members of the Royal College of Physicians of London obtained their degrees in Padua between the foundation of the London College in 1518 and the subsequent 200 years. Even the New World was represented: Edmund Davie was the first American student to obtain his medical degree at Padua in the year 1681!

Surely one of the most famous of the instructors was Galileo Galilei, who went to Padua in 1592 and remained for 18 years. He had been invited to fill the Chair of Mathematics, and his erudition and forceful personality transformed scientific methodology and thought. It was he who taught that experiments were the basis of research and as such initiated modern science. The elevated podium used by Galileo is preserved in all its roughness. He had so many students that they asked that a platform above the ground level be used so that all could hear him. The result was the hastily constructed, inelegant, but serviceable series of steps leading to the platform.

All this past glory is retained at the University of Padua in its several sumptuous galleries and halls. Noteworthy is the Great Hall, whose walls are covered by the coats of arms of the school's innumerable graduates. Also preserved is the beautiful anatomy theater used by Fabricius during his tenure at the university in the mid- and late sixteenth century. The dissecting table was strategically located over a body of water, so that when the authorities came to see whether the illegal practice of human dissection was underway, the body could be dumped into the stream and substituted with that of a laboratory animal.

A visit to this beautiful, ancient, and influential university and its school of medicine would be rewarding for any worker in the health sciences.

Source: Lucia Rossetti, "The University of Padua: An Outline of Its History," 2nd ed. Trieste: Edizioni Lint, 1983.